



**UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/275,883 03/25/99 RENNER

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EXAMINER

HM12/0817

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SCHNITZER B

ART UNIT

PAPER NUMBER

1632

DATE MAILED:

08/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory ActionApplication No.
09/275,883Applicant(s)
Renner et alExaminer
Richard SchnizerArt Unit
1632

— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

THE REPLY FILED Jul 31, 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on Jul 31, 2001. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.
3. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search. (See NOTE below);
- (b) ☐ they raise the issue of new matter. (See NOTE below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☒ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: New claims 128, 132, and 136 present new limitations not previously considered, such as polymerases derived from Bbaru virus, Cabassou virus, Ckikunqunya virus, etc.

4. ☒ Applicant's reply has overcome the following rejection(s):
Claims 75-101 and 103-125 under 35 USC 112, second paragraph.
5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).
6. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached.
7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):
Claim(s) allowed: None
Claim(s) objected to: _____
Claim(s) rejected: 75-101 and 103-125
9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.
10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
11. ☐ Other: _____

DAVE T. NGUYEN
PRIMARY EXAMINER

Art Unit: 1632

ADVISORY ACTION

The request for reconsideration has been considered but does not place the application in condition for allowance because:

The single disclosed species of polymerase does not adequately represent the claimed genus of alphaviral RNA-dependent RNA polymerases, thus the written description requirement is not met for the claimed genus.

The specification fails to teach how to use the invention for therapy in vivo, but discloses no other in vivo use, thus the scope of the invention directed to in vivo use is not enabled. Applicant has pointed to passages in the specification which disclose the use of the invention for expression of polynucleotides in vivo, however Applicant has failed to point to any passage in the specification which discloses a non-therapeutic use for in vivo gene expression. Applicant argues that non-therapeutic in vivo uses were known in the art at the time of filing. This is unpersuasive because these uses must be considered critical elements of the invention which must be disclosed in the specification. Applicant's arguments that gene therapy is not unpredictable are unsupported by evidence.

Applicant indicates that the Office Action implies that non-cytopathic mutations in nsp2 cannot be combined with temperature sensitive mutations in nsp4 to produce a temperature-sensitive, non-cytopathic virus. See page 13 of Paper No. 18. This is inaccurate. The Office Action states that it is not currently possible to accurately predict the effects of mutations on the

Art Unit: 1632

functions of proteins. See page 8 of Paper No. 15. Applicant has presented no evidence that one of skill in the art is capable of making such predictions. Arguments that Lundstrom (2001) successfully made such a mutant are unpersuasive because developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of that filing date. See for example, *in re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). Thus Lundstrom et al is not available as a reference to establish the state of the art at the time of filing. Applicant argues that the effects of mutations at distant sites in the primary structure of a protein, or in different subunits should be additive, and are thus predictable. See pages 14-17 of Paper No. 18. The basis for this argument appears to be that amino acids which are on separate subunits, or are far apart in primary structure, should also be far apart in tertiary structure or quaternary structure. This argument is unpersuasive because it fails to take into account the folding of proteins and subunit interactions. Rudinger teaches that one cannot predict the three dimensional structure of a protein based solely on primary structure data. See page 8 of Paper No. 15. For this reason one cannot know if two amino acids which are distant from each other in the primary sequence of a given protein will also be distant in the tertiary structure. For this reason one also cannot predict how two subunits will interact, and whether two given amino acids on interacting subunits will be proximal to each other. More importantly, there is no basis in the art for predicting the long range structural effects of mutations on protein folding, and such teachings are also absent from the specification. Applicant argues at page 16 of Paper No. 18, that Schnizer et al is not dispositive of the effects of mutations on the claimed nucleic acids. On

Art Unit: 1632

the contrary, Schnizer et al provides an excellent example of the unpredictability of the effects of mutations, as well as the possible long range effects. A single amino acid alteration present in three subunits of a nine-subunit enzyme was shown to destabilize the entire complex. There was no basis in the prior art for predicting such an effect, and there is no basis for predicting which mutations in nsp2 or nsp4 will have long range effects on polymerase structure or on the interaction of subunits. Combined with the teachings of Rudinger, Schnizer et al provides evidence that the effects of mutations on protein structure cannot generally be predicted with accuracy. Applicant presents evidence that mutations which are scattered throughout a protein need not interact functionally, and may have additive effects. However, what is missing from the disclosure, and from Applicant's arguments, is any means of predicting which mutations will be additive and which will not. Because neither the prior art nor the disclosure provide such teachings, one of skill in the art could not make the invention commensurate with the claimed scope.

Applicant argues at page 17 of Paper No. 18 that screening for active polymerases empirically does not represent undue experimentation. This argument was addressed in Paper No. 15, at pages 8 and 9.

Applicant's arguments at page 16 of Paper No. 18 regarding the use of promoters not recognized by Sindbis virus RNA-dependent RNA-polymerase are unpersuasive because, as set forth above, the specification does not enable any polymerase other than a Sindbis virus polymerase.

Art Unit: 1632


Conclusion

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 103-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Richard Schnizer, Ph.D.


DAVE T. NGUYEN
PRIMARY EXAMINER